Perinatal Outcome of Fetal Atrioventricular Block
One-Hundred-Sixteen Cases From a Single Institution

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Background—Fetal atrioventricular (AV) block is an uncommon lesion with significant mortality. Because of the rarity of this disorder, the natural course, extensive evaluation of untreated fetuses, and late follow-up remain unclear.

Methods and Results—Of the 116 consecutive cases of fetal AV block studied from 1988 to 2006, only 1 was terminated, and 75% were live births. Fifty-nine cases of AV block were associated with major structural heart disease, mainly left atrial isomerism (n=40), with only 26% of neonatal survivors. Of the 57 fetuses with normal cardiac anatomy, 41 (72%) were positive for maternal antinuclear antibodies, and 32 of these seropositive mothers did not receive any treatment. This untreated group had live-birth and 1-year infant survival rates of 93% and 90%, respectively. Five fetuses from seronegative mothers showed regression to sinus rhythm during pregnancy. The presence of major structural heart disease, hydrops, an atrial rate ≤120 bpm, and a ventricular rate ≤55 bpm were identified as risk factors for mortality. Logistic regression analysis of the whole group showed that the presence of structural heart disease was the only independent predictor of death (P<0.001).

Conclusions—This long-term study confirms that fetal AV block has a poor outcome when associated with structural heart disease and that spontaneous regression of AV block is possible in seronegative forms. The survival rate of >90% of our untreated patients with isolated forms of AV block raises concerns about any decision to intervene with immunosuppressive agents. (Circulation. 2008;118:1268-1275.)

Key Words: echocardiography □ follow-up studies □ heart block □ heart defects, congenital □ pacemakers □ pediatrics

Congenital atrioventricular (AV) block is an uncommon lesion, first described by Morquio1 in 1901 in several members of the same family. The first description in the fetus was made in 1945, diagnosed by auscultation and ECG.2 Although an ECG can sometimes be recorded in the fetus, interpretation is always difficult. However, with the advance of high-resolution ultrasound equipment, fetal echocardiography has become the method of choice for the diagnosis and analysis of fetal AV block and arrhythmias.3–6 Because of the rarity of fetal AV block, even with more recent published data showing larger fetal series,7,8 the natural course of the disease and late follow-up remain unclear. Moreover, data are lacking that show extensive evaluation of untreated fetuses that were serially monitored with echocardiograms, which makes a critical appraisal of the efficacy of steroid treatment inconclusive. A better understanding of the spectrum and outcome of fetal AV block would facilitate counseling of the parents, patient care, and evaluation of newer therapies.

Clinical Perspective

To provide further information on the outcome of fetal AV block, we describe here a single institution’s experience with a large group of untreated fetuses in a country where interruption of pregnancy is not legally allowed. The consistency of information that results from this long-term study from a single center is unique, especially because we were able to trace the natural history of AV block diagnosed during fetal life.

Methods

Between July 1988 and July 2006, 116 fetuses with congenital AV block were identified from 11 000 referrals for fetal echocardiography at our Fetal Cardiology Unit. The Ethics Committee of the Clinics Hospital of the University of São Paulo Medical School (São Paulo, Brazil) approved this retrospective study. All fetal echocardiographic examinations were performed and reviewed by 1 fetal cardiologist (L.M.L.) whose specialty is...
pediatric and fetal echocardiography through the transvaginal route between 12 and 15 weeks’ gestation (9- to 5-MHz real-time vaginal probe) and the transabdominal route after this period (7- to 2-MHz convex transducer, 5- to 2-MHz sectorial transducer). The fetal heart was examined with standardized imaging techniques incorporating 2-dimensional echocardiography, M-mode, spectral Doppler (pulsed wave), and color Doppler flow mapping. Cardiac rhythm was determined by use of simultaneous M-mode atrial and ventricular wall motion recordings or pulsed Doppler tracings of left ventricular inflow and outflow signals. The gestational age at the detection of heart block was taken as the earliest documentation of the rhythm disturbance. Complete AV block was diagnosed if no mechanical relationship was revealed between atrial and ventricular contractions on M-mode or Doppler echocardiography. Second-degree AV block was diagnosed in the presence of a regular atrial rate with a fixed 2:1 conduction to the ventricles, with special care in the differential diagnosis with premature blocked atrial contractions. All pregnancies were serially followed up by echocardiography to delivery or fetal demise. Pregnancy outcome, postnatal outcome, and late follow-up information were obtained from hospital records, from follow-up questionnaire, or by telephone contact with families or local clinicians. Videotape recordings and digital video clips of all fetal echocardiographic examinations were reviewed to confirm cardiac rhythm, rate, and signs of congestive heart failure and to search areas of persistently increased echogenicity that corresponded to endocardial fibroelastosis. Isolated fetal AV block was defined in the absence of structural heart disease (SHD) related to the heart block.5 Hemodynamically insignificant secundum atrial septal defect and patent ductus arteriosus were considered isolated forms.

Maternal serology was obtained in all cases of isolated AV block, including anti-Ro (SS-A) and anti-La (SS-B) antibodies at the time of the first diagnosis of the AV block. After delivery, this group of mothers, seropositive and seronegative, were advised to seek assistance at our institution if they felt or observed any signs or symptoms of autoimmune disease (arthralgia, myalgia, joint swelling, dry eyes, or dry mouth). Additionally, to search for late seroconversion, seronegative mothers were contacted by phone at follow-up and retested if maternal autoimmune disease was suspected.

During the 18-year study period, our management protocol did not include routine transplacental steroid therapy in isolated fetal AV block, although sympathomimetic therapy was initiated if severe hydrops was present and heart rate was <55 bpm in an effort to salvage the fetus. Complete transplacental treatment with dexamethasone alone (4 or 8 mg/d for 2 weeks, followed by 4 mg/d maintained for the duration of the pregnancy) or associated with a sympathomimetic agent (if the average heart rate declined to <55 bpm) was used recently in a nonrandomized manner in 4 cases. This was done in accordance with the Jaeggi et al9 protocol. We also considered it incomplete treatment when sympathomimetic agents were not associated with dexamethasone or when dexamethasone was used for a few weeks and then discontinued.

To evaluate the presence or absence of diffuse or focal endocardial thickening in the ventricles in this group of isolated fetal AV block consistent with fibroelastosis, fetal and postnatal pathologic reports and available histological sections from autopsy specimens (6 available cases) or an explanted heart (1 patient underwent heart transplantation) were reviewed by 2 pathologists. Linear histological measurements of the endocardial thickness were taken in 3 distinct points of each endomyocardial sample with an image analysis system, and the higher value of each case was compared with normal values obtained from our own data.10

All mothers, even those with fetuses with associated complex cardiac disease, were offered the option of delivery in our tertiary center with active management, including implantation of a pacemaker and surgical intervention in the newborn when necessary. Fetal diagnosis of AV block was confirmed by postnatal ECG, echocardiography, catheterization, or necropsy. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analysis

Data are presented as frequencies, mean and SD, or median with range. Comparisons between groups were performed with the χ2 test to analyze the influence on neonatal outcome of associated SHD, hydrops, maternal autoimmune disease and antinuclear antibodies, atrial rate, and ventricular rate. After identifying by univariate analysis the factors that influenced mortality, we included these factors in a logistic regression analysis (multivariate model). The unpaired Student t test was used to compare atrial and ventricular rates in surviving and nonsurviving fetuses. Kaplan–Meier estimates were used to plot survival curve, and log-rank tests were used to compare fetuses with and without cardiac defects. Odds ratio calculations were done with odds ratio generator version 1, free edition. All tests were 2 sided, and values of P<0.05 were considered statistically significant (SPSS version 13, SPSS Inc, Chicago, Ill).

Results

During the 18 years of the study, in the total group of 115 pregnant women, 116 fetuses were diagnosed as having congenital AV block. Fifty-nine AV blocks were associated with SHD; 57 were isolated forms mostly associated with autoimmune antibodies (Table 1). Two fetuses were twins, and both were affected. The major indication for fetal echocardiography was bradycardia during a routine obstetric scan. The median gestational age at the time of diagnosis of the AV block was 29.5 weeks (range, 10 to 40 weeks); the median maternal age was 27 years (range, 15 to 42 years).

Of the 115 pregnancies (116 fetuses, including twins with AV block), only 1 pregnancy was terminated, and live births equaled 75% (n=86). Late follow-up was possible in 57 of 59 patients (97%) who survived the neonatal period. Fetal and neonatal deaths correlated significantly with the presence of SHD (15 of 59 surviving, 43 of 56 nonsurviving; P<0.001), hydrops (1 of 59 surviving, 26 of 56 nonsurviving; P<0.001), an atrial rate ≥120 bpm (9 of 59 surviving, 32 of 56 nonsurviving; P<0.001), or a ventricular rate ≤55 bpm (15 of 59 surviving, 33 of 56 nonsurviving; P<0.002).

Atrial rate ranged from 57 to 180 bpm and ventricular rate from 25 to 90 bpm. Mean atrial and ventricular rates were higher in surviving than in nonsurviving fetuses (137±14 versus 117±23 bpm, P<0.0001; 63±10 versus 52±11 bpm, P<0.0001, respectively). Logistic regression analysis of the whole group showed that the presence of SHD was the only independent predictor of death (P<0.001). To date, no further deaths have occurred (Figure 1).

Fetal AV Block Associated With SHD

Clinical Features

Fifty-nine fetuses with AV block had associated SHD, mostly left atrial isomerism (n=40, 68%) or discordant AV and ventriculoarterial connections (n=8). We also documented cases of hypoplastic right ventricle (n=3), ventricular septal defect (n=4; 1 associated with coarctation), double-inlet left ventricle (n=2), tetralogy of Fallot (n=1), and rhabdomyomas (n=1). High-definition fetal echocardiography allowed 5 precise diagnoses before 15 weeks in patients referred to us after the first trimester examination.
because of sustained bradycardia (Figure 2). In addition to bradycardia as an indication for fetal echocardiography, 1 mother was diabetic and gave birth to a newborn with a discordant AV connection, and 2 mothers had a previous child with SHD (a left atrial isomerism followed by left atrial isomerism and a trisomy 21 with ventricular septal defect followed by left atrial isomerism). Two other fetuses had increased nuchal translucency.11

Progression of AV Block
Of the 59 fetuses, 45 (76%) had complete AV block, and 14 (24%) had second-degree AV block. Of the 14 fetuses with second-degree AV block, 6 (42%) had progression to complete AV block during fetal life (fixed form in 4, alternating with periods of second-degree AV block in 2), 7 remained at the same rhythm until birth (2 fetal deaths), and 1 regressed to sinus rhythm. In this group of 4 live births with second-degree AV block, follow-up showed progression of the heart block in all patients and 2 late deaths. Only 2 patients with discordant AV connection are alive and well at 11 and 15 years.

Spontaneous Regression of AV Block
One fetus at 32 weeks gestation was diagnosed as having ventricular septal defect associated with coarctation and second-degree AV block with sinus rhythm at 36 weeks’ gestation. After birth, the child died of respiratory failure 1 year after surgical repair of coarctation and ventricular septal defect (case 5, Table 2).

Outcome
As shown in Table 1, of the 59 fetuses with AV block, only 1 pregnancy was terminated; live births equaled 60% (n=35);

Table 1. Characteristics of 116 Fetuses With Congenital AV Block

<table>
<thead>
<tr>
<th>Cause</th>
<th>Isolated AV Block (n=57)</th>
<th>AV Block With SHD (n=59)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at diagnosis, wk</td>
<td>29 (18–40)</td>
<td>29 (10–39)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial rate, bpm</td>
<td>136.3±17.9</td>
<td>119.1±21.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ventricular rate, bpm</td>
<td>58.6±13.6</td>
<td>56.9±11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hydrops, n (%)</td>
<td>11/57 (19)</td>
<td>16/59 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Late cardiomyopathy/EFE, n (%)</td>
<td>2/57 (3)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>No treatment, n (%)</td>
<td>46/57 (81)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Transplacental therapy, n (%)</td>
<td>11/57 (19)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Steroid only (dexamethasone), n (%)</td>
<td>2/57 (3.5)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Steroid + sympathomimetic, n (%)*</td>
<td>4/57 (7)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Sympathomimetic only, n (%)</td>
<td>5/57 (9)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Termination of pregnancy, n (%)</td>
<td>0</td>
<td>1/59 (1.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Fetal death, n (%)</td>
<td>Yes 6/57 (10)</td>
<td>23/58 (40)</td>
<td></td>
</tr>
<tr>
<td>No (live birth)</td>
<td>51/57 (90)</td>
<td>35/58 (60)</td>
<td></td>
</tr>
<tr>
<td>Neonatal death (≤28 d), n (%)</td>
<td>7/51 (14)</td>
<td>20/35 (57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Neonatal survivors, n (%)</td>
<td>44/57 (77.1)</td>
<td>15/58 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-Ro positive</td>
<td>32/41 (78)</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Ro negative</td>
<td>12/16 (75)</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up after neonatal period, n (%)</td>
<td>42/44 (95)</td>
<td>15/15 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Permanent pacemaker (≥28 d), n (%)</td>
<td>18/51 (35)</td>
<td>18/35 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>Permanent pacemaker (&gt;28 d), n (%)†</td>
<td>11/31 (35)</td>
<td>2/17 (12)</td>
<td>NS</td>
</tr>
</tbody>
</table>

GA indicates gestational age; EFE, endocardial fibroelastosis.
*Two patients treated for 3 weeks and withdrawn.
†After exclusion of 2 lost to follow-up and 1 termination.
Late follow-up was possible in all patients. At the end of the neonatal period, 15 newborns were still alive. Hydrops was found on the diagnostic fetal echocardiogram in 27% of the fetuses. Fetal and neonatal deaths correlated significantly with the presence of left atrial isomerism (4 of 15 surviving, 35 of 43 nonsurviving; \( P = 0.001 \)), with 90% mortality at the end of the neonatal period and no survivors after 3 months of follow-up. Patients with discordant AV connection had 25% mortality at the end of the neonatal period. Logistic regression analysis of this group showed that hydrops, an atrial rate \( \leq 120 \) bpm, and a ventricular rate \( \leq 55 \) bpm were not independent predictors of death (\( P = 0.05 \)).

A permanent pacemaker was implanted in 57% of all live-birth patients (20 of 35), 18 in the neonatal period and 2 after this period (from 3 months to 1 year). Last follow-up showed 7 survivors, 5 paced and 2 not paced (from 2 to 10 years of age).

**Heart Rate**

Atrial rate ranged from 62 to 180 bpm, and ventricular rate ranged from 32 to 90 bpm. One case of fetal AV block associated with left atrial isomerism presented transient and intermittent atrial flutter that resolved spontaneously with an atrial rate of 465 bpm alternating with a lower atrial rate of 80 bpm.

Mean atrial rate was significantly lower in this group, although the ventricular rate was not significantly different between fetuses with and without SHD. After exclusion of 40 fetuses with left isomerism from the group with SHD, mean atrial rate also was not significantly different in surviving and nonsurviving fetuses (137±13 versus 129±24 bpm; \( P = 0.0691 \)), although the ventricular rate remained different (62±10 versus 49±14 bpm respectively; \( P < 0.0001 \)). Fetuses with left atrial isomerism had a slow atrial rate (112±20 bpm) consequent to the known sinus node dysfunction and had 100% mortality despite all active management, including surgical intervention and implantation of a pacemaker when necessary.

### Isolated Fetal AV Block

#### Clinical Features

Fifty-seven fetuses had isolated AV block. The major indication for fetal echocardiography was bradycardia. Two mothers had a previous child with AV block, and 1 fetus was the result of in vitro fertilization in a seronegative mother. Forty-one women (72%) were seropositive for antinuclear antibodies, most often anti-RO (SS-A) antibodies, and 15 women were seronegative (1 mother of twins, both with AV block). Of the 41 seropositive mothers, 36 were positive at the time of fetal diagnosis of heart block, and 5 (12%) had late seroconversion detected from 1 to 8 years after delivery. In this isolated AV block group, hydrops was present at first examination in 11 fetuses (19%), and 5 mothers had a known diagnosis of systemic lupus erythematosus, 2 of Sjögren syndrome, and 1 of arthritis.

#### Progression of AV Block

Of the 57 fetuses, 35 had complete AV block, and 22 (38%) had second-degree AV block. The incidence of second-degree AV block was higher in fetuses with isolated AV block compared with the fetuses with SHD (n=14). Of the 22 fetuses with second-degree AV block, 9 (16%) had progression to complete AV block during fetal life (fixed form in 5, alternating with periods of second-degree AV block in 4), 9 remained at the same rhythm until birth, and 4 regressed to sinus rhythm.

### Table 2. Prenatal Findings and Postnatal Outcome of Fetuses With Congenital Heart Block Followed by Regression to Sinus Rhythm

<table>
<thead>
<tr>
<th>Case</th>
<th>GA at Diagnosis, wk</th>
<th>Maternal Antibodies</th>
<th>Rhythm</th>
<th>Atrial Rate, bpm</th>
<th>Ventricular Rate, bpm</th>
<th>Associated SHD</th>
<th>GA at Regression to Sinus Rhythm, wk</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Negative</td>
<td>2:1 Alternating with complete AV block</td>
<td>154</td>
<td>77</td>
<td>No</td>
<td>23</td>
<td>Alive/well at 9 y</td>
</tr>
<tr>
<td>2*</td>
<td>18</td>
<td>Negative</td>
<td>2:1 AV block</td>
<td>150</td>
<td>75</td>
<td>No</td>
<td>20</td>
<td>Alive/well at 4 y</td>
</tr>
<tr>
<td>3*</td>
<td>18</td>
<td>Negative</td>
<td>2:1 AV block</td>
<td>154</td>
<td>77</td>
<td>No</td>
<td>21</td>
<td>Alive/well at 4 y</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>Negative</td>
<td>2:1 AV block</td>
<td>150</td>
<td>75</td>
<td>No</td>
<td>22</td>
<td>Alive/well at 2 y</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Negative</td>
<td>2:1 AV block</td>
<td>136</td>
<td>63</td>
<td>VSD + COAO</td>
<td>36</td>
<td>Respiratory failure and ID at 1 y</td>
</tr>
</tbody>
</table>

GA indicates gestational age; VSD, ventricular septal defect; COAO, coarctation of the aorta; and ID, infant death.

*Twins.*

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**Figure 2.** Tricuspid atresia and hypoplastic right ventricle in a fetus at 13 weeks gestation. Top, Four-chamber view demonstrating hypoplastic right ventricle. Bottom, M-mode echocardiography showing complete AV block. Atrial rate was 108 bpm; ventricular rate, 50 bpm. Black arrows indicate atrial wall; white arrows, ventricular wall. RV indicates right ventricle; LV, left ventricle; RA, right atrium; and LA, left atrium.
sinus rhythm. In this group of 9 live births with second-degree AV block, late follow-up showed no progression of the heart block in only 3 patients: 2 were alive and well at 8 years and 3 months, and 1 had sudden death at 7 years.

**Spontaneous Regression of AV Block**

Four fetuses regressed to sinus rhythm, 3 from second-degree AV block and 1 from second-degree AV block alternating with third-degree AV block (Table 2 and Figure 3). All mothers were repeatedly seronegative for anti-RO/LA antibodies. The median gestational age at the time of diagnosis of the AV block was 18 weeks (range, 18 to 20 weeks); the median maternal age was 25 years (range, 25 to 33 years). Two fetuses were dizygotic twins (cases 2 and 3), and both had second-degree AV block at 18 weeks that reverted to permanent sinus rhythm after 1 and 3 weeks, respectively.

The time between the diagnosis of AV block by fetal echocardiography and regression to sinus rhythm ranged from 1 to 5 weeks. After this period, all fetuses had permanent sinus rhythm during fetal life until birth. Long-term follow-up showed all infants in sinus rhythm, alive and well (cases 1 through 4, Table 2).

**Outcome**

As shown in Table 1, of the 56 pregnancies (57 fetuses, twins with AV block), no pregnancy was terminated, and live births equaled 89% (n=51). Late follow-up was possible in 95% of patients who survived the neonatal period (n=42 of 44).

In fetuses with normal cardiac anatomy, fetal or neonatal death was not related to the presence or absence of anti-RO (SS-A) antibodies (29 positive anti-RO of 38 surviving, 11 of 17 nonsurviving, \( P > 0.05 \); 9 negative anti-RO of 38 surviving, 6 of 17 nonsurviving, \( P > 0.05 \)).

A permanent pacemaker was implanted in 29 of all patients (excluding 2 lost to follow-up), 18 during the neonatal period and 11 after this period (from 33 days to 7 years). Twenty paced patients (69%) had third-degree AV block on the initial diagnostic echocardiogram, and 9 (31%) had second-degree AV block that progressed to third degree and low heart rates. In contrast, of the 20 live-born neonates who were not paced and were followed up, only 9 of 20 (45%) had complete AV block on the initial diagnostic fetal echocardiogram. The last follow-up showed 38 survivors, 21 paced and 17 not paced (from 1 month to 18 years of age).

**Heart Rate**

Atrial rate ranged from 57 to 170 bpm; ventricular rate ranged from 25 to 85 bpm. Atrial rate \( \leq 120 \) bpm was not related to death in fetuses with normal cardiac anatomy. Logistic regression analysis of this group showed that hydrops, an atrial rate \( \leq 120 \) bpm, and a ventricular rate \( \leq 55 \) bpm were not independent predictors of death \( (P > 0.05) \).

**Management: Conservative Approach Versus Treatment in Isolated AV Block**

In 46 of 57 cases of isolated AV block (32 related to maternal autoimmune antibodies, 14 seronegatives), no treatment with dexamethasone or sympathomimetic drugs was attempted, with a live-birth rate of 91% (95% confidence interval [CI], 83 to 99) and a 1-year survival rate of 89% (95% CI, 80 to 98). If we consider the incompletely treated fetuses plus the untreated ones \( (n=53) \) to avoid the bias of excluding some of the most affected fetuses, the live-birth and 1-year survival rates still remain 83% (95% CI, 73 to 93) and 81% (95% CI, 70 to 92), respectively. The 32 seropositive untreated fetuses had live-birth and 1-year survival rates of 93% (95% CI, 85 to 100) and 90% (95% CI, 80 to 100), respectively. Incompletely treated plus untreated fetuses \( (n=38) \) had live-birth and 1-year survival rates of 84% (95% CI, 73 to 96) and 81% (95% CI, 69 to 94).

In 7 fetuses, treatment was considered incomplete. Two mothers had already been taking dexamethasone for 3 weeks when referred to our institution. This treatment was withdrawn because of maternal edema \( (n=1) \) and after the fetal echocardiogram showed no signs of ventricular dysfunction or congestive heart failure. Both infants are alive and well. Sympathomimetic agents without steroids were attempted in 5 fetuses (initiated directly in the umbilical cord in 4) because of a ventricular rate \( \leq 55 \) bpm and hydrops, with no survivors. In an attempt to increase fetal heart rate, 4 of 5 mothers were given isoproterenol \( (0.05 \) to 0.1 mg/min directly in the umbilical vein and then maintained intravenously or orally), and 1 of 5 was given terbutaline orally \( (2.5 \) to 5.0 mg over 4 hours). These treatments caused a temporary increase in fetal ventricular rate \( (5 \) to 20 bpm), with a return to initial levels after a short time despite medication \( (from 1 \) to 5 days).
Nonrandomized complete transplacental treatment with dexamethasone and sympathomimetic agents, according to the treatment protocol of Jaeggi et al.,9 was used in 4 patients with ventricular rates ≤55 bpm. Severe hydrops was present in 2 cases, and ventricular dysfunction plus mild hydrops was present in 1. The other fetus had a heart rate of 55 bpm with no signs of heart failure or ventricular dysfunction. We observed that despite treatment, ventricular rates continued to fall in all fetuses, with 3 deaths during the fetal/neonatal period. Ventricular function improved in 1 fetus that was not accompanied by an improvement in hydrops. Of these 4 cases, the only survivor was the nonhydropic fetus, born by cesarean delivery indicated at 34 weeks’ gestation because of severe oligohydramnios.

Late Onset of Cardiomyopathy

Of the 41 fetuses with antibody-associated AV block, visible areas of persistently increased echogenicity on the fetal echocardiogram that could eventually correspond to endocardial fibrosis were present in 3 patients, 2 described as having a multiple echogenic foci by the second-trimester ultrasound examination. The postnatal clinical course of these 3 patients showed late onset of dilated cardiomyopathy in 2 (5%); 1 died 5 years after cardiac transplantation, and the other is alive with symptoms of congestive heart failure (ejection fraction, 30%). The other infant is alive and well with no endocardial thickening visualized by 3-dimensional echocardiography.

Necropsy study of the explanted heart showed thickening of the left ventricular endocardium (204 μm compared with 47 μm of the right ventricle; normal value, ~30 μm).10 Of the 16 deaths in the isolated AV block group, 11 were associated with anti-RO antibodies. Pathology examination of the heart was available in 7, all showing some degree of endocardial thickening caused by fibrosis and elastosis with no evidence of myocarditis.

Discussion

In the present study, we describe the largest reported single-institution experience with AV block in fetuses (n=116), highlighted by 98% of late follow-up and by the fact that only 1 pregnancy was interrupted. In this review, we have identified isolated forms (49%) and forms associated with SHD (51%). As described by Schmidt et al.,3 our results show a relation between poor outcome and hydrops, ventricular rate ≤55 bpm, and associated SHD. An atrial rate ≤120 bpm was significantly associated only with left isomerism, and the dismal prognosis observed was related more to this structural heart lesion than to the low atrial rate itself. However, the presence of SHD was the only independent predictor of death.

The mortality rate was 74% at the end of the neonatal period in the 59 patients with SHD, and left isomerism was by far the most prevalent disease (40 of 59), with 100% mortality during the first year of life. Although this high mortality rate was previously reported in 3 earlier series,3,7,8 varying from 83% to 60%, the growing number of terminations reported compared with our data are probably creating a bias toward better mortality rates because the worst cases tend to be excluded. This seems to be confirmed in a series with a better mortality rate of 60% at the end of the neonatal period associated with a termination rate of 69%.8 Because we had only 1 case of interruption, our results are nearer the natural history of the disease compared with others with a higher termination rate (17%,3 33%,7 and 69%).8

With the wide use of screening for chromosomal abnormalities by measurement of fetal nuchal translucency between 11 and 14 weeks’ gestation, it has been easy to detect congenital AV block in abnormal fetal hearts at earlier stages of pregnancy because the conduction abnormality develops earlier compared with the isolated forms of AV block.11 Fetal echocardiography performed through the transvaginal route allowed adequate images of the AV septal defect in 3 patients and the hypoplastic right ventricle in 1 patient. It was also possible to diagnose 2:1 AV block in a 10-week-old fetus by using wall motion by M-mode and superior vena cava/aortic flow by Doppler imaging. Intracardiac anatomy was not clear at this point, but 3 weeks later, we could see a huge rhabdomyoma obliterating the left ventricle.

Isolated AV block in the fetus has been widely documented, and the high association with maternal antibodies was present in our series (41 of 57, 72%). It was interesting to observe that only 36 mothers were positive at the time of fetal diagnosis of heart block (63%) and 5 had late seroconversion (9%). Although anti–SS-A (RO) antibodies/anti–SS-B (LA) usually maintain a stable profile for many years, late seroconversion has been observed without a clear explanation.12 Insensitive methods, a very low concentration of maternal antibodies, or even a true variation in antibody levels has been speculated to explain this phenomenon. Late seroconversion in those patients reinforce the possibility of other unknown intrinsic (fetal) or extrinsic (maternal) factors involved in the genesis of AV block besides anti–SS-A (RO)/anti–SS-B (LA) antibodies. Moreover, other studies have proved that maternal antibodies are not sufficient to cause AV block because the prevalence is low in seropositive mothers, from 1% to 7.5%.13 The unclear role of maternal antibodies is also proven in our experience, with the 2 intriguing cases of dizygotic twins: only 1 affected twin by AV block born to a seronegative mother who had late seroconversion and arthritis 3 years after delivery, and another seronegative mother with both twins affected by second-degree AV block at 18 weeks (cases 2 and 3, Table 2).

Very limited data are available on the progression and regression of AV block, which could add some important information with respect to developmental aspects of this rhythm disturbance. Second-degree AV block was present in 36 fetuses (31%) at initial examination and invariably progressed to complete AV block during fetal or postnatal life (95% until the recent follow-up). In contrast, spontaneous regression of heart block is quite rare, although it has been reported in 4 fetuses with structurally normal hearts.14 In our series, 5 fetuses from seronegative mothers showed regression to sinus rhythm (1 with SHD). The first
patient in whom remission was observed was seen 10 years ago and had 2:1 AV block alternating with complete AV block. Steroid therapy was offered to the parents to avoid progression to the complete form. They refused the therapy, and the fetal rhythm was surprisingly normal in the following echocardiogram performed after 5 weeks. If steroid therapy had been accepted, we could certainly conclude that this treatment was responsible for the remission. Thereafter, another 4 cases of spontaneous regression were observed, raising important questions about the irreversible nature of AV block. It was also a very interesting experience to diagnose 2:1 AV block in both dizygotic twins at 18 weeks that reverted to permanent sinus rhythm in 1 and 3 weeks. A possible explanation for this phenomenon is the parasympathetic dominance before 30 weeks’ gestation, which could lead to AV block if the stimulation is pronounced in the AV node.14

Several studies have proposed that treatment with fluorinated steroids, especially dexamethasone, results in benefits to the fetuses affected by seropositive antibody-mediated AV block.9,15–18 The most striking difference between the present study and those previously published concerns the positive impact of steroid therapy. Unlike the study by Jaeggi et al,9 our untreated patients did not have such an unfavorable outcome, with live-birth and 1-year survival rates similar to those in their treated group (91% versus 95% and 89% versus 90%, respectively). The benefits of treatment were blurred when we used the data from a previous study published by Jaeggi et al9 (n=21, 2 fetal deaths and 1 neonatal death) and compared the results with the sample of untreated patients in this work. The odds ratio of staying alive after the neonatal period for those who received treatment with dexamethasone was 0.731 (95% CI, 0.16 to 3.4). These differences could be explained by the limitations described in the Jaeggi et al study such as a small number of cases treated in a nonrandomized protocol and dependent on the era of the diagnosis. The better outcome could be explained by the improvement in intensive care facilities, not by the introduction of dexamethasone in the management of this group of patients. Moreover, antenatal steroids have risks such as oligohydramnios, maternal hypertension, and fetal decreased brain growth, thus increasing obstetric complications.19 The development of oligohydramnios and maternal edema in 2 patients was consistent with the complications of steroid therapy. Despite this discrepancy, it is agreed that in some specific cases, especially the hydropsic ones, steroids could have some benefit, and further investigations are necessary.

Conclusions

The present long-term study confirms that approximately half of fetuses with AV block had associated major SHD, with a high prevalence of left isomerism and a dismal prognosis. The other group had a significantly better prognosis and was represented by fetuses without SHD, associated mainly with maternal autoimmune antibodies that are usually positive at the time of fetal diagnosis, although late seroconversion also was documented in a small number of cases (12%). Seronegative fetuses showed a prognosis similar to that of seropositive fetuses and surprisingly had spontaneous regression of AV block in a few cases, associated or not with SHD.

This study also indicates that steroid therapy seems not to have an effect on the natural history of fetal autoimmune-related AV block and should help to improve the patient selection for this kind of treatment. A large-scale, prospective, multicenter trial addressing the efficacy and safety of this treatment would be beneficial.

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Disclosures

None.

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Congenital atrioventricular block is a rare finding, occurring in ≈1 in 11,000 to 20,000 live births. With the advent of fetal echocardiography, congenital heart block has been identified earlier in life. Even with more recent published data showing larger fetal series, the natural course of the disease and late follow-up remain unclear. Moreover, data are lacking that show extensive evaluation of untreated fetuses that were serially monitored with echocardiograms, which makes a critical appraisal of the efficacy of steroid treatment inconclusive. A better understanding of the spectrum and outcome of fetal atrioventricular block would facilitate counseling of the parents, patient care, and evaluation of newer therapies. To provide further information on the outcome of fetal atrioventricular block, we describe here the experience of a single institution with a large group of untreated fetuses in a country where interruption of pregnancy is not legally allowed. The consistency of information that results from this long-term study from a single center is unique, especially because we were able to trace the natural history of atrioventricular block diagnosed during fetal life. The present study also indicates that steroid therapy seems not to have an effect on the natural history of fetal autoimmune-related atrioventricular block and should help to improve the patient selection for this kind of treatment. A large-scale, prospective, multicenter trial addressing the efficacy and safety of this treatment would be beneficial.
Perinatal Outcome of Fetal Atrioventricular Block: One-Hundred-Sixteen Cases From a Single Institution
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In the article by Lopes et al, “Perinatal Outcome of Fetal Atrioventricular Block: One-Hundred-Sixteen Cases From a Single Institution,” which appeared in the September 16, 2008, issue of the journal (Circulation. 2008;118:1268–1275), the following correction should be made.

In the Abstract, Methods and Results, line 5, the live birth and 1-year infant survival rates are incorrect and should read, “93% and 90%, respectively.”

The error has been corrected in the current online version of the article.

The publisher regrets the error.

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